Medical Staff Conference

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Advances in the Treatment of Carcinoma of the Breast

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *At Medical Grand Rounds this morning we are going to have a presentation on advances in the treatment of carcinoma of the breast.*

Case Summary

DR. BOZDECH:† The patient is a 47-year-old married woman who operates a beauty shop and is the mother of an 8-year-old son. She was referred to the University of California San Francisco Medical Center for a second consultative opinion regarding adjuvant chemotherapy for carcinoma of the breast. In January 1975, while in good health, she felt "lumpiness" in the upper outer aspect of her left breast and went to her gynecologist, who could not identify a specific lesion. However, in May 1975, on a repeat examination by her gynecologist, a firm mass with some skin fixation in the axillary tail of the left breast was found. The patient said there was no history of nipple discharge or bleeding. She had been taking birth control pills for about eight years and had regular but scant periods.

On October 5, 1975, she was examined by a consulting surgeon who confirmed the presence of a 2.5 by 3 cm firm mass with skin fixation in the upper outer quadrant of the left breast. He did not think the mass was fixed to muscle, and he felt no nodes in the left axilla. On October 8, 1975, a modified radical mastectomy was carried out. During the axillary dissection no evidence of enlarged nodes was apparent. A frozen section showed the presence of adenocarcinoma; a permanent section showed infiltrating ductal carcinoma, with 1 out of the 18 nodes dissected positive for disease. Further studies, which included a bone scan, bone survey and a right xeromammogram, gave negative findings. Results of liver function tests were within normal limits. From November to December 1975 radiotherapy to the lower axilla, internal mammary chain and left anterior chest wall was carried out. There was a total dose of 4,000 rads to the areas mentioned and concurrent radiation to the left supraclavicular and apical axilla to 4,500 rads, plus a boost to the internal mammary chain. The only complication from this therapy was some dermatitis with local edema.

In June 1976 the patient consulted an oncologist in her community about having chemotherapy and he advised her against it. On July 21, 1976, she came to the University of California Medical Center seeking corroboration of his opinion and there were no symptoms present at that time. Her past history was unremarkable, there had been no other operations or illnesses, and there was no

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family history of breast cancer. Vital signs were normal; findings on physical examination were entirely unremarkable, with no evidence of local recurrence, adenopathy, hepatomegaly, bony tenderness or weight loss. Minimal laboratory studies done at that time gave findings within normal limits. The patient was advised, the referring physician was also notified and the patient went home to consider this advice.

DR. SMITH: *Thank you for that summary, with its somewhat Delphic implication. As you know, this is a very common problem in an area in which there has been tremendous controversy. We are very pleased to have Michael Friedman from the Cancer Research Institute to discuss this case and to tell us what advice was given and why.*

DR. FRIEDMAN:* This case represents a very perplexing medical, social and moral problem. The patient is an articulate, intelligent and attractive woman who is apparently free of all disease and who has received the benefits of multiple medical consultations. The radiotherapist who administered chest wall irradiation feels strongly that adjunctive chemotherapy is needed. She consulted an experienced oncologist who feels equally strongly that it would be inappropriate to give adjunctive chemotherapy at this time. Therefore, the patient came to our clinic for a further opinion and there was a further muddying of the waters. Rather than simply defending our advice to her, I would like to review some of the information from clinical and laboratory studies that helped us arrive at our decision. In retracing this thinking we can judge some of the virtues and vices of the various approaches to the adjuvant treatment of primary breast cancer that are used today.

We should begin with a brief review of some of the general aspects of tumor kinetics as described by Skipper.[1] The growth characteristics of a population of tumor cells varies with its mass. The growth of tumor masses can be described by a mathematical model (Figure 1); the general behavior of many tumors can be fitted to this Gompertzian curve. In very small tumors the mass of cells is small, individual cell growth is rapid, the doubling time is short and the fraction of growing cells is high. As tumors progressively enlarge, growth slows and a plateau state is reached. Small, early tumors grow rapidly (almost logarithmically); older larger tumors grow slowly.

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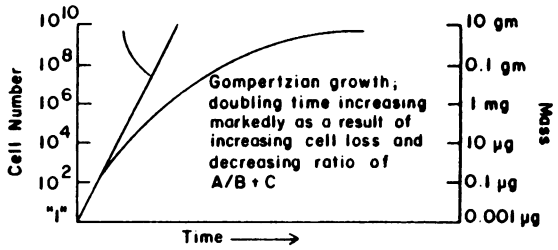

Figure 1.—The growth characteristics of populations of tumors. (Reproduced with permission from Cancer[1])

In order to describe the behavior of specific cellular components of tumors, we must consider a model proposed by Skipper and Zubrod.[2] They have arbitrarily allocated the tumor cells comprising a neoplasm into four compartments: A, B, C and D (Figure 2). Compartment A cells are those that are proliferating and are clonogenic. They are able to make new progeny and they divide rapidly. These are the predominant cells in small early tumors, those undergoing the log phase of growth. Compartment B cells are nonproliferating; they are not at the moment producing progeny, but they could initiate mitotic activity at any time. There is presumably free communication between cells of these two compartments (A and B). Larger tumors are composed mostly of B compartment cells. These cells often have a long T_{G1} (Gap 1) or are resting in the T_{G0} (Gap 0) phase of the cell cycle. Compartment C consists of cells that are nonclonogenic. They are viable and metabolically active, but unable to produce progeny. Compartment C is a repository for cells either from compartment A or B, but having once lost their proliferative ability these cells never regain it. Of course cells die and can be imagined to be in compartment D—of no further clinical interest.

The significance of this sort of an intellectual model is related to what it offers us clinically. Small tumors are mostly composed of proliferating cells (compartment A cells) and are sensitive to the drug and radiation therapy currently available. Larger tumors, made up of B compartment cells, represent a much more difficult clinical problem. These tumors are incompletely and inefficiently dealt with by conventional radiation therapy or chemotherapy. Certainly these modalities have some efficacy, but the cells are not nearly so sensitive as are the compartment A cells. Compartment C cells represent another sort of problem. These are cells that may not be truly malignant because they cannot produce. They may cause anatomic or architectural problems—a tu-

mor in the brain made up of compartment C cells, for example, would remain a problem—but this is an issue of practical rather than intellectual importance.

Utilizing these two concepts, Gompertzian growth kinetics and cellular compartments, we can imagine the biological path along which breast cancer proceeds. In an early tumor with rapid log phase growth, most cells are compartment A cells. These cells are rapidly proliferating and are very sensitive to the drugs and radiation therapy available. As the tumor becomes progressively larger, detectable by the relatively gross means at our disposal, it is composed primarily of compartment B cells. This tumor cell population is much more difficult to treat. Surgical operation remains the treatment approach that most efficiently removes compartment B cells and effectively deals with T_{G0} resting cells. After surgical "debulking" any remaining neoplastic cells become proliferating, compartment A cells. One of the most effective ways of perturbing cells to proliferate is simply to reduce the size of compartment B, thereby removing growth inhibition. One can imagine shifting back along the tumor growth curve into a phase where there is more rapid cell division.

Dr. Howard Skipper has raised some intriguing questions about malignancies in general, and breast cancer in particular.[1] To paraphrase these, first of all, after radical surgical procedures for breast cancer what fraction of patients still bear occult clonogenic tumor cells that can lead to recurrence? Clearly a recurrence of breast cancer leads invariably to death. Once disease is recurrent, the woman's fate is sealed. The only curative procedures at our disposal are surgical operation and, in rarer instances, radiation therapy for the primary tumor. Second, for those patients who bear some clonogenic tumor cell burden after operation, what is the number of these cells and what happens to them? Elegant investigations done at the time of operation have shown malignant-looking cells in peripheral venous blood which have been loosed at the time of surgical operation.[3] It is reasonable to imagine that if these cells have been loosed before operation you can also find them circulating in the peripheral blood. However, surgical operation is curative; therefore, even though these cells are being continually shed there must be mechanisms—possibly immunologic—that deal with these small numbers of cells and prevent them from becoming metastatic growths that kill the patient. Third, how can we deal with these clonogenic cells with the most effective available therapies? And finally, is it possible to utilize data on the natural history of breast cancer to identify a group of women who stand a much higher risk of recurrent disease postoperatively? That is, are there useful predictors which indicate which patient is likely or unlikely to have a local or distant recurrence?

We are all aware of the fact that breast cancer is a common problem in our community and it is probably increasing in frequency. There are approximately 75 new cases of breast cancer each year per 100,000 women and 27 women of that 100,000 will die of breast cancer.[4]

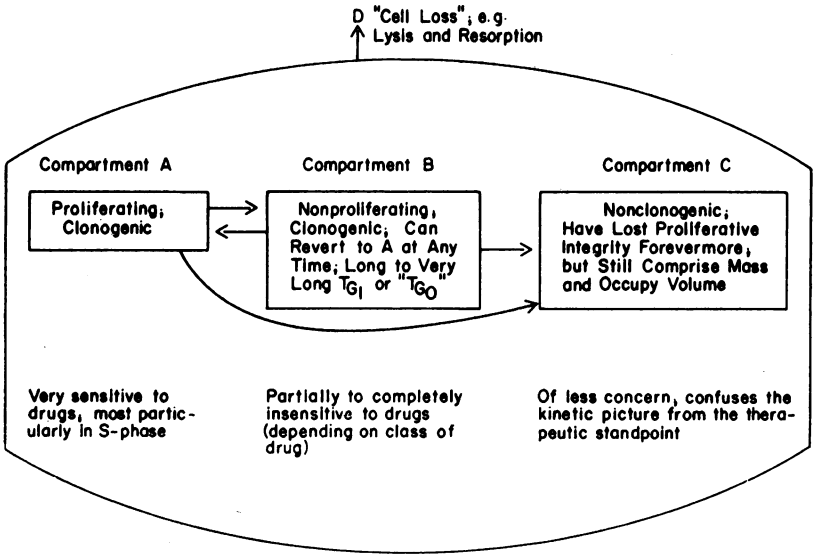

Figure 2.—Postulated populations of malignant cells within a tumor. (Reproduced with permission from Cancer[1])

The crucial natural history aspects of this disease are depicted graphically in Figure 3. Stage I disease is early breast cancer characterized by lesions that are 2 cm or less in the breast with no clinical axillary node involvement. Only 17 percent of all women with breast cancer are in this stage at the time of presentation. The prospect for five-year survival (this does not mean five-year cure) is relatively good; 85 percent of these women are alive five years later. But even in this group of women who have an excellent prognosis, a proportion will be dead in five years. Stage II disease is a much more common presentation. The tumors are larger, up to 5 cm, and there may

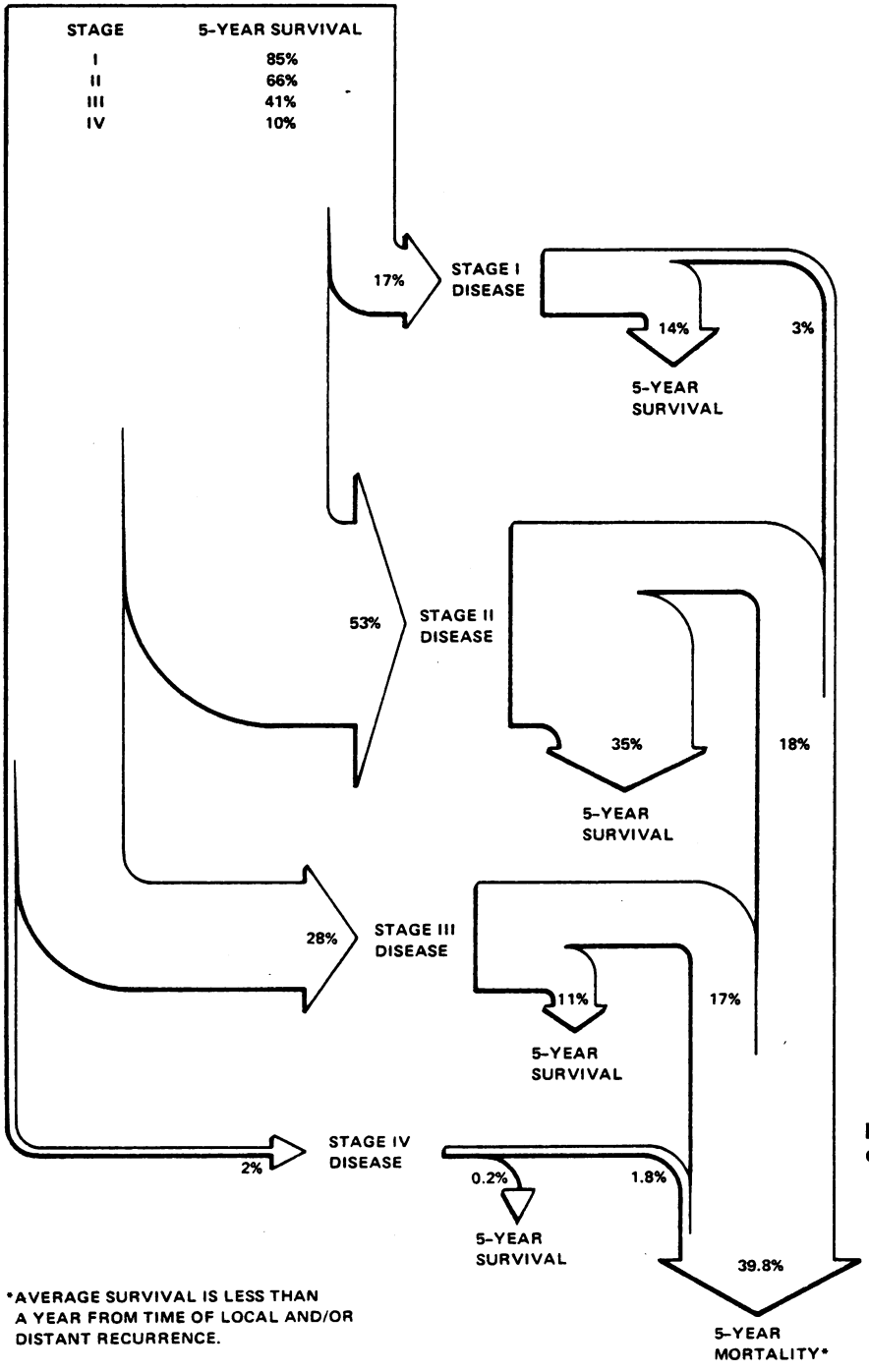

Figure 3.—Natural history of cancer of the breast in women.

TABLE 1.—*Recurrence Rate After Surgical Operation for Breast Cancer**

Nodal Status	Time After Operation (Recurrence Rate in Percent) 18 Months	36 Months	60 Months
1-3 positive	13	37	53
≥4 positive	52	68	80
All positive	33	53	67
Tumor >6.0 cm and 1-3 positive nodes	24	..	63
Tumor >6.0 cm and ≥4 positive nodes	62	..	94

*Based on information from Fisher and Slack.[5]

or may not be axillary node involvement on the same side. Again two out of three of the women do well, but a third of them die of breast cancer. Stage III disease is more advanced. The tumor is larger than 5 cm, most often the axillary contents are involved, and more than one out of two of these women still die of breast cancer (even with adequate surgical procedures on the breast). Stage IV disease is that which is metastatic at the time of operation and the five-year survival is low in this group of women. These figures indicate whether to expect a woman having a certain stage of breast cancer to live for five years with or without disease.

The patient we previously described has stage II disease. The primary lesion was modest in size, but one of 18 axillary lymph nodes was involved. Her chance of living five years is two out of three. But by the same token there is a one in three chance of recurrence of breast cancer and of death from it. It is always difficult to apply broad statistical trends to individual patients.

Of the 90,000 new cases of breast cancer each year, perhaps 40 to 50 percent of the women will have axillary nodes involved and this is the best, the simplest and the most important discriminant we have clinically. In one of his early studies, Fisher and his associates[5] asked the question: "If the axillary lymph nodes are involved after curative surgery, does the number of nodes involved make any difference in the recurrence rate?" Table 1 shows that when one to three axillary nodes are involved, 13 percent of the women have recurrences within a year and a half, increasing to almost 50 percent by five years. At ten years, the number is slightly greater. If more than four nodes are positive, a much more rapid recurrence pattern occurs. In half of the women there are recurrences at a year and a half, progressing to 80 percent by five years. The size of the primary tumor also is significant; in women with large primary tumors and more than four positive axillary nodes there is a recurrence rate of between 90 and 100 percent. Even if there are no axillary lymph nodes involved, in 5 percent of these women there will be a recurrence at 18 months. At five years, in 21 percent there is a recurrence, and by ten years in 25 percent of these women there is recurrent breast cancer. Thus, in the group of women who are at lowest risk, there is a one in four chance of recurrent disease developing.

Philosophically, the efficacy of surgical operation as a modality must be reevaluated. It certainly cures many women primarily, it gives us crucial information about the stage of the breast cancer, but we know that it may be insufficient therapy in perhaps 40 to 50 percent of all women. It is unlikely that any advance in surgical technique alone will improve the likelihood of disease-free survival. Since the introduction of the radical mastectomy by Halsted[6] in the latter part of the last century, the ability to deal with the primary tumor has been progressively improving. Surgeons are careful and competent in resecting local breast disease. The clinical problems of breast cancer, however, are of a more widespread nature. It is not the local disease that is difficult to control, it is the metastatic disease. Results of a clinical experiment have shown this clearly: Women having radical mastectomies were randomized postoperatively to receive radiation therapy to the chest wall or to receive nothing. Comparing their ultimate survival there was no difference between the two groups; that is, even though patients in whom both surgical operation and radiation therapy were done had fewer chest wall recurrences, their overall survival was unaffected. At similar rates both groups died of disseminated breast cancer.[7] These data intimate that breast cancer is a disseminated disease process and that it is not surgical failure that causes recurrences, it is the nature of the disease. Unless this disease is considered a systemic one from the beginning, attention is improperly focused on keeping the chest wall clear of disease while the patient dies.

Does this sort of thinking about the biology of breast cancer have implications for surgical studies? It certainly does. What the best surgical procedure may be for breast cancer has been a hotly contested issue, but this controversy is assuming less and less importance. The best operation depends on what the patient wants and what the surgeon wants. The classic principles of on-

cologic surgery hold true no matter what the setting. One must remove all of the primary tumor and one must have proper staging. Once those two demands are satisfied, it matters less what sort of surgical operation is done. There may be some instances in which a lumpectomy with axillary node dissection followed by radiation therapy or chemotherapy, or both, is equivalent to a radical or a modified radical mastectomy. I think that the type of newspapers one sees in grocery stores are going to have to search for another hot item of controversy because this one really has been exhausted. Surgical operation is an important modality in breast cancer, but it is insufficient in many cases. The logic is irrefutable, then, that adjunctive therapy with surgical operation should save more women, if we have effective adjunctive therapy.

Are there reasons to believe that there exist for adjunctive therapy animal model systems that would be applicable to humans? After a laboratory animal is inoculated in the thigh with a transplantable tumor, the tumor predictably metastasizes to the lung and kills the animal. If treated with chemotherapy the animal's survival time may be prolonged, but it will still die of disseminated disease. If the primary tumor is surgically removed, the animal will die, again of disseminated disease (because it had already metastasized at that point). But if the two manipulations are carried out together, that is if the recently inoculated tumor is resected and chemotherapy is administered, the animal can be cured.[8] This is a very persuasive model system that is of more than veterinary interest. A number of human malignant diseases: osteogenic sarcoma, embryonal rhabdomyosarcoma of childhood, Wilm's tumor of childhood and Burkitt's lymphoma have been successfully treated with this strategy. These are diseases in which it is abundantly clear that adjunctive therapy, that is surgical operation or radiation therapy plus effective chemotherapy, measurably adds to control of disease. This is an optimistic background for clinical trials in breast cancer.

In evaluating treatment of patients with breast cancer, several concerns must be addressed. First of all, systemic therapy should be contemplated for patients who are receiving "curative surgical procedures," for these procedures are not always curative and furthermore we can predict which patients are at added risk for having recurrent disease. The failures that occur represent breast cancer already disseminated at the time of surgical operation. Removing the tumor is necessary but insufficient therapy. Since it is impossible to detect occult disease after operation, we must treat blindly and systemically, and with the most effective agents possible. Second, the biologic and kinetic considerations mentioned earlier should be recalled. The contemporary approach has as its objective the destruction of all tumor cells by repetitive courses of chemotherapy. However, chemotherapy kills tumor cells at a rate that is best described as first order. That is, if a therapy kills 99 percent of a tumor the second course of that therapy, assuming that no drug resistance emerges, will kill 99 percent of the remaining cells, and so forth. A fixed proportion of cells is killed each time, not an absolute number. We can anticipate that by continued treatment, all cells could be ultimately eliminated. We know that advanced breast tumors contain cells that have relatively low growth fractions; they are at the plateau phase of their growth, they have long cycle times.[1] Many of the cells are nonclonogenic and therefore, are relatively insensitive to the therapies we use.

A third concern is whether we can provide sufficiently aggressive chemotherapy without endangering the patient's life. The goal is to kill 100 percent of the tumor; that is laudable and may be necessary. In an aggressive attempt to eradicate all tumor cells, we must realize that the drugs used are toxic and the side effects of these drugs are a well-recognized danger. There is a finite chance that a patient is going to die due to unpredictable drug toxicity. Such a mishap could result from a dose error on the part of the patient, on the part of the druggist or on the part of a prescribing physician. It could result from individual intolerance by that patient of a "usual" dose of chemotherapy. To have a patient die of toxicity would be a very distressing thing indeed, especially when a proportion of the women we are discussing are cured of breast cancer by surgical operation alone. It would be unacceptable to have many deaths secondary to an attempt to "rescue" even more of the women. Clearly, there are high risk groups of patients, women with large tumors or many axillary nodes involved, with whom these risks need to be negotiated. One out of five women with negative axillary nodes is fated to have recurrent breast cancer; even in women with the smallest risk of recurrence the question of whether

or not adjuvant therapy should be included needs to be considered.

We have some information from previous, older trials with adjuvant chemotherapy that may help us interpret the two new trials which I would like to discuss. In 1957 Dr. Fisher[9] began his first cooperative trials with breast cancer, and at that time he began studying cases of women who had primary resections for breast cancer which appeared to be curative. In his first study the methodology was a very simple one—postoperatively half the women were given a placebo and half were given an alkylating agent of known effectiveness, thiotepa. The patients were given the thiotepa only on the day of surgical operation and on the two subsequent days because it was thought that the dissemination of disease was an intraoperative event, and attempts were directed toward killing the cells circulating at the time of operation. At that time chemotherapy was thought to operate by zero order rather than first order kinetics, and it was presumed that a short course of chemotherapy could kill all the cells. Furthermore, little was known about the cell cycle of breast cancer cells; it was thought that they divided very rapidly and that a short course of therapy would be very appropriate.

Many of our concepts have subsequently changed, but even based on these serious methodologic flaws some important information came out of this trial. After a number of years the two groups were evaluated and when all the patients were pooled, there was no overall difference in rate of survival or recurrence. However, when a subpopulation of the treated group were extracted —in this case the premenopausal women who had four or more axillary nodes involved—there was a very significant advantage shown for that high risk subgroup. After many years (this study has been closed for more than ten years now), this group had still fared significantly better than the control group. It is not so noteworthy that this was a negative study. It is much more interesting that there were any positive results. Using chemotherapy in a less than optimal fashion, Fisher was still able to show some advantage for a highly selected group of patients. Since then, there have been several intraoperative and perioperative trials like this, utilizing alkylating agents or 5-fluorouracil. All of these studies have deficiencies in design, statistical analysis and methods of follow-up or staging.

In recent trials investigators have attempted to remedy some of these objections and have been cognizant of the following factors: The primary neoplasm and the regional nodes should be surgically removed because of the biological relationship between tumor size, host offense, and chemotherapy response. Patients are stratified according to the presence of histologically positive axillary nodes (associated with an increased incidence of recurrence). Chemotherapy should be started as quickly as possible after surgical operation, but continued for a long period, presumably to encompass many of the times for doubling of those cells. Prolonged adjunctive therapy has been very effective in other kinds of clinical human malignancy. First order cell kinetics apply to characterize the effective killing of cells by chemotherapy, and certainly we would like to include drugs that have proven efficacy in metastatic disease, presuming them to be more effective in earlier microscopic disease than in later disease. Additionally, chemotherapy should be administered intermittently to allow for as little immunosuppression as possible. Finally, the regimen should be safe, there should be no known long-term complications of the treatments, whatever toxicities there are should be minimal, predictable, reversible and not life-threatening. Treatments should be given to women as outpatients in order to interfere as little as possible with their lives.

TABLE 2.—*Clinical Trial of Prolonged Therapy with L-phenylalanine Mustard (L-Pam) as an Adjuvant to Surgical Operation in Breast Cancer**

Age 49		*Age 50-75*	
L-PAM	**PLACEBO**	**L-PAM**	**PLACEBO**
0.15 mg/kg/d P.O.×5 Q 6 weeks		0.15 mg/kg/d P.O.×5 Q 6 weeks	

*Based on information from Fisher B, Carbone P, Economou SG, et al.[10]

The first study I would like to describe in some detail is a more recent study of Dr. Fisher's[10] which utilized L-phenylalanine mustard (L-Pam®) as the chemotherapeutic adjuvant (Table 2). Women were divided into premenopausal and postmenopausal age groups (none were older than 75) and were randomized to receive either a placebo or L-phenylalanine mustard. The dosage was 0.15 mg per kg of body weight per day for five days, given every six weeks, for a total time of 18 months. These patients had no evidence of metastatic disease at the time of surgical operation. The study was begun in September

1972; it was terminated in January 1975, and the statistical analysis is still being done. During this period about 400 patients were randomized in the trial and in the most recently published data about 150 patients in each arm of the protocol were evaluated. In general the toxicity was infrequent and mild (only 10 percent of those administered doses). Leukopenia was infrequently noted. A third of the women who received the L-Pam had nausea and vomiting, but 11 percent of the placebo-treated women had the same symptoms. Most of the women felt that it was a very tolerable program. In the first published report of this data, there was a significant benefit for the L-phenylalanine mustard treated group. An overall comparison of the placebo groups and the L-phenylalanine mustard groups showed that treatment in 22 percent of the placebo group and in 10 percent of the L-Pam group had failed. A separate analysis of postmenopausal women showed a statistically significant difference at the 0.01 level. No statistical significance in the premenopausal control group was shown, but there was a trend favoring better control of disease for those women in the premenopausal group who were treated with L-phenylalanine mustard.

More recent evaluations of these data have been made (follow-up studies have been done on some of the women for more than five years), and unpublished reports substantiate the preliminary data for the postmenopausal group. Of all the L-phenylalanine mustard treated group, treatment failed in 17 percent compared with 25 percent for the placebo group. Dividing these groups into premenopausal and postmenopausal women, the failure rate for the premenopausal placebo group was 30 percent and for the L-phenylalanine mustard group 11 percent ($p<.001$). For postmenopausal women the placebo had a 19 percent failure rate and L-phenylalanine mustard a 23 percent failure rate. One possible conclusion is that use of L-Pam is ineffective in preventing malignant recurrence. However, L-phenylalanine mustard has a real impact on this disease, and one might presume that for premenopausal women this drug as a single agent is appropriate therapy for high risk groups. Based on these data L-Pam appears to be inappropriate therapy for postmenopausal patients. These data represent large numbers of patients from many institutions and are carefully handled; but breast cancer is a chronic malignant disease and, as such, evaluation at two or even five years may be insufficient. Full analyses at 10, 15 and 20 years must be made before we can draw definitive conclusions. This analysis of the data may comfort those who criticized this National Surgical Adjuvant Breast Program (NSABP) study as being prematurely published. There is an intellectual difficulty in deciding when a study is ripe for evaluation and publication, and when data should be distributed to the general medical community for their use.

TABLE 3.—*National Cancer Institute Milan, Italy Breast Cancer Adjuvant Study.* CMF is abbreviation for cyclophosphamide (Cytoxan®) methotrexate and 5-fluorouracil*

SURGERY *With Positive Lymph Nodes, 2-4 Weeks*	
"CMF"	**NO FURTHER TREATMMENT**
Cytoxan®, 100 mg/m² P.O. day 1-14 5-fluorouracil 600 mg/m² } I.V. days 1 & 8 Methotrexate 40 mg/m² } 12 courses given at 4 week intervals	

*Based on information from Bonadonna G, Brusamolino E, Valagussa P, et al.[11]

The other major study that demands our attention is that of Bonadonna and his associates[11] at the National Cancer Institute of Milan. The study is similar to the NSABP trial; stratification was based on menopausal age and nodal involvement. In all patients curative breast surgical operation was done (axillary nodes were involved in all patients), half of the group received combination chemotherapy, the other half nothing further. CMF chemotherapy (a combination of three drugs: cytoxan, methotrexate and 5-fluorouracil) was used in this study. This is a therapy of known efficacy in women with metastatic breast cancer. It is more aggressive than single agent L-Pam therapy (and one might expect it to be *a priori* several fold more effective). It is associated with a 60 percent response rate in women with metastatic disease, in contrast to L-phenylalanine mustard which has a 20 percent response rate. Table 3 shows Bonadonna's intermittent schedule of therapy; pulses are given in four week cycles for 12 months.

L-Phenylalanine mustard was employed in the NSABP trial because the investigators did not want to expose patients to excessive toxicity. L-Pam can be given easily and safely. Patients taking this drug usually do not experience cystitis or alopecia. The toxicities encountered in Bonadonna's study were generally mild. Myelosuppression was noted in about half the patients, and conjunctivitis in

20 percent of the patients. There were no life-threatening toxicities and no toxic deaths occurred. Clearly, CMF chemotherapy is more toxic than use of L-Pam and the question is, "Was that extra toxicity therapeutically worth it?" An unpublished update of the information of this study indicates that use of CMF appears to be strikingly beneficial. The study has been in progress for only three years, but approximately 30 percent of both control premenopausal and postmenopausal women have had recurrences. By contrast, in the CMP-treated premenopausal women there has been an 8 percent failure rate. In the CMF-treated postmenopausal women, 15 percent have had recurrences. Both groups are highly different statistically. Apparently both the premenopausal and the postmenopausal women benefit from therapy. To date there do not seem to be any peculiar aspects of the recurrence patterns for either the CMF or control treated groups. In neither the CMF nor the L-Pam trial has there been any increased incidence of a second malignant disease, but of course it is premature to draw a definite conclusion from that datum. Most women find adjuvant chemotherapy to be tolerable, and the improvement in disease-free survival is dramatic.

It is possible that the magnitude of these differences will not persist at five- and ten-year analyses, but it seems likely that significant benefit will be evident. Adjuvant chemotherapy makes an important impact upon the natural history of breast cancer—a disease that otherwise has proved to be ultimately fatal. These preliminary reports are persuasive and satisfying.

In summary, there are several conclusions that can be drawn from this information:

- Arguments concerning the relative merits of different surgical procedures for breast cancer have become less engaging. It is apparent that both local and systemic approaches are necessary for complete therapy.
- Careful clinical trials will be needed to evaluate newer methods of dealing with local disease (surgical and radiation therapy techniques) and systemic disease (different combinations of chemotherapy and hormonal therapies varying dose, schedule and duration of treatment).
- As systemic therapy becomes more effective, perhaps less radical surgical operation will be equivalent to more radical procedures.
- Once the short- and long-term toxicities of adjuvant chemotherapy can be assessed (and no unacceptable toxicity is detectable), patients with negative axillary nodes should be treated with adjuvant therapy to attempt to improve their known 25 percent failure rate at ten years.

REFERENCES

1. Skipper HE: Kinetics of mammary tumor cell growth and implications for therapy. Cancer 28:1479-1499, Dec 1971

2. Skipper HE, Zubord CG: Some thoughts concerning cancer and cancer therapy. Med Tribune Med News 9:11 and 16, 1968

3. Fisher B, Slack NH, Boss IDJ: Cancer of the breast—Size of neoplasm and prognosis. Cancer 24:1071-1080, Nov 1969

4. Silverberg E, Holleb AI: Cancer statistics. Cancer 21:13-31, Jan 1971

5. Fisher B, Slack NH: Number of lymph nodes examined and prognosis of breast carcinoma. Surg Gynecol Obstet 131:79-88, Jul 1970

6. Halsted WS: Results of operations for the cure of cancer of the breast performed at Johns Hopkins Hospital from June, 1889 to January, 1894. Ann Surg 20:497, 1894

7. Fisher B, Slack NH, Cavanaugh PJ, et al: Postoperative radiotherapy in the treatment of breast cancer—Results of the NSABP clinical trial. Ann Surg 172:711-732, Oct 1970

8. Skipper HE: Some thoughts on surgery-chemotherapy trials against breast cancer, *In* Monograph, Southern Research Institute, Birmingham, Ala, 1971, pp 1-13

9. Fisher B, Ravdin RG, Ausman RK, et al: Surgical adjuvant chemotherapy in cancer of the breast—Results of a decade of cooperative investigation. Ann Surg 168:337-356, Sep 1968

10. Fisher B, Carbone P, Economou SG, et al: l-Phenylalanine mustard (L-Pam) in the management of primary breast cancer—A report of early findings. N Engl J Med 292:117-122, Jan 16, 1975

11. Bonadonna G, Brusamolino E, Valagussa J, et al: Combination chemotherapy as an adjuvant treatment in operable breast cancer. N Engl J Med 294:405-410, Feb 19, 1976